REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claim 1 has been cancelled and replaced by new independent claim 27, which is identical is scope to original claim 1 except that Z has been limited to -O- and -S- by the removal of -NH- from the definition Z, and reference to C_{1-6}fluoroalkyl has been removed from the listed substituents on Q^2 in the definition (i)1) for the group Q^1X^1- (page 29 of the above amendments) and from the listed substituents on one or both of Q^{13} and Q^{14} in the definition (i)9) for the group Q^1X^1 (page 31 of the above amendments), and additionally reference to C_{1-6}haloalkyl has been removed from the definitions of Q^{15} and Q^{21} in definitions (ii) and (iii) (page 32 of the above amendments), all in relation to the proviso in claim 1 (now claim 27 beginning near the top of page 29 of the above amendments).

Claim 27 also differs from original claim 1 in that all parenthetical phrases objected to by the Examiner have been removed, solely as an accommodation to the Examiner in the hope of advancing the prosecution of this application. Reformatting (hanging intended paragraphs etc.) has been used to regain the clarity lost by the removal of the parentheses, and "which cyclic group" in relation to with reference to substituents on heterocyclic ring D at various points throughout claim 27 has been changed to "which heterocyclic group," for greater specificity to regain clarity that was lost by removal of the parentheses. The overall effect of the removal of the parentheses and the reformatting is intended and believed to be totally neutral on the scope and meaning of the claim. However, the extensive number of minor amendments required to remove all these parentheses dictated the replacement of original claim 1 with new and reformatted claim 27. Certain of the dependent claims have been also been amended to remove parentheses to which it is thought the Examiner is objecting, to the extent feasible without compromising the clarity of these claims.

The dependent claims have been amended as necessary to refer to new independent claim 27 in place of cancelled claim 1, and the multiple dependencies of original claims 4, 7, 8 and 9 have been removed. All dependencies and multiple dependencies of the present claims are believed to be in proper form.

Claim 11 has been amended to remove "C_{1-4}fluoroalkyl" from the definition of the at least one substituent on Q^2 in group 1), and from the definition of the at least one substituent on at least one of Q^{13} and Q^{14} in group 9), all within the definition of one of R^{2a} and R^{2b} at pages 6 and 8 of the above amendments.

Claim 13 has similarly been amended to remove "C_{1-4}fluoroalkyl" from the definition of the one substituent on Q^2 in group (a)1) within the definition of the "other" of R^{2a} and R^{2b} that is not methoxy, at page 11 of the above amendments.

Compound claims 14 and 15 have been amended to delete compounds that are no longer within the scope of the claims as amended above.

The last portion of process claim 19 has been amended to replace the subjective "is required" with respect to whether a salt is formed by making it an optional step.

"Use" claim 21 has been cancelled as not being in a format generally accepted under U.S. practice.

Method claim 22 has been amended to remove the recitation of "such as a human being," which expression of merely an example or preference within a previously recited group is not generally acceptable under US practice.

It should be clear from the above that no new matter has been added by these amendments, and entry thereof is respectfully requested. Following entry of these amendments, claims 2-20 and 22-27 remain pending in this application.

Claim Rejections - 35 USC § 112

Claims 1-13, 18-22, 25 and 26 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner identifies 13 "reasons" (a) through (m) for this rejection, which reasons will be summarized below in sequence, followed by Applicants' response:

Reason a: The limitations within parentheses are not clear whether or not they are part of the claims.

Response: Applicants and the undersigned believe that the claims are clear as originally written, and that any person skilled in the art would understand that the parenthetical phrases are identifying the variables of the immediately preceding claim recitation, and that the use of parentheses makes the claims far clearer than if not used. It is believed that the Examiner is inappropriately extrapolating the principle that the use of parentheticals *in the nature of preferences or examples* in a claim of that which precedes is not favored under US practice. It would be clear to any skilled person that the moiety definitions within the parentheses of the present claims are most certainly a part of the claims, and it is respectfully submitted that under no reasonable interpretation could they be considered as simply examples or preferences within the scope of the preceding definition.[1] Nevertheless, the objected-to parentheses have been removed and replaced by reformatting (such as hanging indents) as an accommodation to the Examiner to advance the prosecution of this application, even though the claims before this amendment were believed to have been in a proper format and clear in meaning to the skilled person. Withdrawal of this ground for rejection is therefore respectfully requested.

Reason b: In the definition of R^5, groups 2-4, 6-8, 10-17, 20-22 are unclear as to where the point of attachment is. The Examiner cites, as an example, the group "C_{1-5}alkyl$X^2C(O)R^{11}$" (in group 2), questioning whether it would attach to the quinazolinyl ring through the alkyl group or through R^{11}. Likewise, the Examiner asserts that it is unclear how groups 3, 4, 6-8, 10-17 and 20-22 are attached to the quinazolinyl ring.

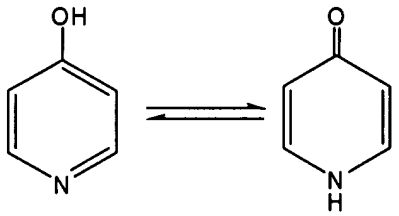
Response: It is respectfully submitted that the point of attachment of R^5 is clear from the claims when properly interpreted in light of explanations given in the specification. The Examiner attention is respectfully drawn to the passage at page 57 line 18 to page 58 line 27 which explains how the various groups connect. R^5 is clearly always linked to X^1 and X^1 in turn is always linked to the quinazoline ring. See also claim 1 wherein the substituent on the quinazoline ring is denoted as "R^5-X^1-". Therefore in group 2) wherein R^5 is

[1] The *only instance* of such an objectional preference or example was the phrase "such as a human being," which has now been removed from method claim 22.

"C_{1-5}alkyl$X^2C(O)R^{11}$", it is the C_{1-5}alkyl group that is bound to X^1, X^1 is bound to the quinazoline ring and R^{11} is the terminal moiety.

Reasons c and d: Within the same definition (group 9) the Examiner objects to the recitation of "pyridone" which is said to be a narrow limitation followed by the broad limitation of "5-6-membered aromatic heterocyclic group... ," commenting that it is unclear which limitation is intended for R^{80}.

Response: It is respectfully submitted that the definition in group 9) is clear. The recitation of "a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S" is clearly appropriate in this claim, and is not at all in the nature of the "such as" wording objected to in the cases cited by the Examiner in Reason d. The reason for specifying pyridone separately in this instance is out of recognition that pyridones exist in isomeric form:



so that while they still have extensive aromatic character they may not be considered to be "aromatic" in the purest definition of the term. Accordingly, it is not only appropriate, but necessary, to separately recite "a pyridone group" in this claim to make clear Applicants' intent that both isomeric forms are encompassed by the claims.

Reason e: In the definition of Q^1, the Examiner asserts that it is unclear how groups 2-10 are attached to ring C or the quinazolinyl ring, questioning whether these groups would attach to the rings through the alkyl group or through Q^2, or Q^{14} (for group 9), or Q^{14a} (for group 10).

Response: It is respectfully submitted that the point of attachment of Q^1 is clear. The Examiner's attention is again drawn to the specification passage at page 57 line 18 to page 58 line 27 which explains how the various groups connect. Thus for group 9), "C_{1-4}alkylQ^1 $(C_{1-4}alkyl)_j(W^2)_kQ^{14}$" it is the C_{1-4}alkyl group that is bound to X^1 and X^1 is bound to the

quinazoline ring or to ring C and Q^1 is the terminal moiety. The skilled person is presumed to have read the specification, which provides clear guidance, if there is any question from the claim, as to the manner of attachment.

Reason f: The Examiner questions the phrase in claim 1, "or R^1 can be selected from any of the groups defined herein" and asserts that "it has indefinite metes and bounds because R^1 can be a monvalent group represented by ring C, R^5, R^{28}, R^{29}, R^{54}, or R^{55}, etc. as well as a divalent group represented by Z, X^1 , W^3, W^4, etc.," and further comments that the scope of anyone of the variables is not the same, and thus, it is unclear what the intended scope for R^1 is."

Response: It appears that the Examiner is suggesting that the phrase might be interpreted as meaning that R^1 can have the combined meaning of *each and every moiety defined in the entire claim.* It is respectfully submitted that a reasonable skilled person would well know that this could not possibly be the intended meaning, and would clearly understand that R^1 in context of this portion of the claim may have any of the definitions provided elsewhere in the claim *for* R^1. Nevertheless, to expedite the prosecution of this application, this phrase has been supplemented to recite "for R^1". Any possible basis for this ground for rejection has thus been overcome.

Reason g: The Examiner asserts that "the limitation of R^2 as '6,7-methylenedioxy or 6,7-ethylenedioxy' is not clear unless two of R^2 form such a ring. If one R^2 has two dioxy groups, then there will be an incomplete valence. Clarification is solicited.

Response: It is believed that the skilled person reading this claim would understand without doubt or question that in addition to the other recited values for R^2 in claim 1, that the R^2 substituent on the quinazoline ring is exactly what is stated, that is a 6,7-methylenedioxy or 6,7-ethylenedioxy substituent that binds at both the 6- and 7-positions of the quinazoline ring. Clear confirmation of this is found, *e.g.*, in Example 47 and see also page 35 lines 15-16 where it states that R^{2a} and R^{2b} together form 6,7-methylenedioxy or 6,7-ethylenedioxy.

Reason h: The Examiner asserts that claim 2 lacks antecedent basis for reciting R^{1a} as an "oxo" group, which is said not to be recited in claim 1.
Response: Claim 2 does not lack antecedent basis, the compounds of claim 2 lie within the scope of claim 1. R^{1a} in claim 2 represents a subset of the values of R^1 in claim 1, and R^1 can be "oxo" because claim 1 states that "R^1 represents hydrogen, oxo, halogeno," etc. Therefore, the basis for this ground for rejection is not understood.

Reason i: The Examiner asserts that claim 19 lacks antecedent basis for reciting R^5 as "$C_{1-5}alkylR^{113}$", which is said to not be recited in claim 1. The Examiner further asserts that many variables such as R^{114}, R^{115}, R^{116}-R^{120}, R^{127}, R^{128}, etc. are not recited in claim 1 either.
Response: Claim 19 is a process for the preparation of a compound according to claim 1 of the formula I, and necessarily recites a number of new variables in order to describe the processes for the preparation of these compounds. Each new variable. *e.g.* $R^{113-126}$ is defined in the claim, and each corresponds to a subset of a previously defined variable or variables. For example group 3) of process d) is "$X^{20}C_{1-5}alkylX^5R^{22}$", which corresponds to group 4) in the definitions of R^5 in claim 1 and thus the new variable X^{20} is defined as a subset of the values of X^4 and the new variables $R^{118-120}$ are defined as for R^{23}, R^{26} and R^{27}. It is therefore respectfully submitted that claim 1 has proper antecedent basis as a process for the preparation of a compound of claim 1.

Reason j and Response: Applicants recognize that claim 21 is in a "use" or "second medical use" format, which is not generally accepted under U.S. practice. Therefore, claim 21 has been cancelled, rendering this ground for rejection moot.

Reason k: The Examiner notes that claim 22 recites a "method for producing an antiangiogenic and/or vascular permeability effect" which she asserts "has indefinite metes and bounds because it is unclear what disease is treated (*i.e.*, hypertension or cancer?)."
Response: The phrase "production of an antiangiogenic and/or vascular permeability reducing effect" would be readily understood by a person skilled in the art who would immediately appreciate that said medicament can be used to treat pathological conditions that

are mediated by angiogenesis and/or increased vascular permeability. It is well understood by a person skilled in the art that undesirable or pathological angiogenesis has been associated with a number of disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma, as stated in the description on page 1 lines 11-17 of the present specification. See also specification page 2 lines 15-21 for a discussion of diseases associated with pathological angiogenesis and/or increased vascular permeability.

Vascular endothelial growth factor (VEGF) is known to be a key stimulus for vasculogenesis and angiogenesis. Phase III clinical trials of bevacizumab, a monoclonal antibody to VEGF, have validated VEGF as a target in both colorectal cancer (CRC) (Hurwitz *et al*, 2004[2] and Giantonio *et al*, ASCO 2005[3]) and non-small cell lung cancer (NSCLC) (Sandler *et al*, ASCO 2005[4]).

Reason 1: Claims 5, 25 and 26 are said to be indefinite insofar as they recite the term "azaindole," which the Examiner asserts has indefinite metes and bounds because it is not clear what the maximum number of ring nitrogen is, or their locations.
Response: The Examiner's attention is called to the definition of the term azaindolyl on page 56, lines 19-22 of the specification, and therefore its structure is clear. It should further be noted that 5-bromo-7-azaindole is compound 14 on page 72, where a scheme for its preparation is described.

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[2] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* **350:** 2335-2342

[3] Giantonio, BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB, High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study 3200 J Clin Oncol **23**, 16S, abstract 2, 2005

[4] Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, Johnson DH. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial - E4599. Abstract No. LBA4. 2005 ASCO Annual Meeting Proceedings.

Reason m: Claims 2-13 and 18-22 are (also) rejected as being dependent on claim 1 and carrying over indefinite limitations.

Response: Inasmuch as it is believed that the grounds for rejection of claim 1 have been overcome, this ground for rejection has been overcome as well.

Claim Rejections -35 USC § 101

This ground for rejection of claim 21 has been obviated by the cancellation of claim 21.

Claim Rejections - Obviousness-Type Double Patenting

Various of the claims have been *provisionally* rejected for obviousness-type double patenting over one or more of Applicants' assignees' copending applications No. 10/494,137; 10/494,388; and 10/344,678. Inasmuch as all of these applications are in active prosecution and no claims have yet been allowed, it is premature to take a position on the distinctions of the preset claims over the claims what will eventually issue in from those applications. Accordingly, Applicants will defer their response to these grounds for rejection until and if claims issue in those applications before claims are in condition for allowance in the present application.

It is noted, however, that the PCT application of which U.S. application No. 10/344,678 is the U.S. National Stage published as WO 02/16352 on February 28, 2002, whereas the International Application from which the present application derived has a filing date of January 28, 2003. Thus, disregarding for the moment the UK priority application of the present application that was filed on February 1, 2002, the publication of WO 02/16352 could be considered 102(a) prior art. Nevertheless, the present claims, as amended, are clearly structurally and patentably distinct from the disclosure of WO 02/16352 inasmuch as the present claims are now limited to Z being -O- or -S- whereas the linker at the 4-position of the compounds of WO 02/16352 is -NH-. However, applicants reserve the right to assert entitlement of the claims to the priority filing date of the priority application of the present

application, and furthermore reserve the right to swear behind the publication date of WO 02/16352 insofar as it may be considered to be section 102(a) prior art.

Claim Rejections -35 USC § 102

Claims 1-10 and 18-22 have been rejected under 35 U.S.C. 102(b) as being anticipated by Hennequin *et. at.* (WO 00/47212). The Examiner notes that on pages 54-58, Hennequin disclose several quinazoline compounds that are substituted with indolyl-oxy at the 4th position, and also substituted with a group such as 3-(pyrrolidin-1 yl)propoxy or 3 piperidinopropoxy, etc., referring to compounds on lines 31 and 32 of page 57, and also to compounds #25 and 26 in Table I at page 115, which the Examiner describes as quinazoline substituted with indazolyl-amino.

The Examiner's attention is drawn to the proviso in claim 27 (also in claim 1) that one or more R^1 and/or one or more R^2 are selected from one of the five groups defined thereafter (appearing in new claim 27 beginning at page 29 of the above amendments). The Examiner is also reminded that an anticipation rejection most generally requires the prior art disclosure of *at least one specific compound* that directly falls within the scope of the present claims.

It is believed that by reason of the above amendments, there is not even any generic overlap between the present claims and the disclosure of the Hennequin *et al.* reference, no less any disclosure in Hennequin *et al.* that would give rise to an anticipation. Therefore, it is respectfully requested that this ground for rejection be withdrawn.

Claim Rejections -35 USC § 103

Claims 1, 5-13, 14-17, 23 and 24 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hennequin *et. al.* It is respectfully submitted that by reason of the above-noted proviso in what is now claim 27, and claim amendments as noted above, that there is no generic overlap between the present claims and the disclosure of Hennequin *et al.* Accordingly, in the absence of any overlap, it is respectfully submitted that not even a serendipitous selection and combination of the multitude of alternatives for each variable disclosed by Hennequin *et al.* could achieve a compound falling within the scope of the

present claims. Accordingly, no case of *prima facie* obviousness in view of Hennequin has been made with respect to the presently claimed invention, and withdrawal of this obviousness ground for rejection is believed to be in order and is respectfully requested.

Conclusion

It is believed that each ground for rejection has been addressed and overcome by the above Amendments and/or the foregoing Remarks. Accordingly, withdrawal of each ground for rejection and allowance of all claims are believed to be in order and are respectfully requested.

Information Disclosure Statement

The Examiner's attention is drawn to the further Information Disclosure Statement being filed herewith, together with a form PTO-1449 and copy of each non-US patent documents cited therein. Consideration of these documents and acknowledgement of same is respectfully requested by return of an initialed copy of the PTO-1449 to the undersigned.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: September 30, 2005 By: _____

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